## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | The impact of gestational weight gain and pre-pregnancy body mass index on the prevalence of large-for-gestational age infants in two cohorts of women with Type I Insulin-Dependent Diabetes: A cross-sectional population study |
| **AUTHORS** | McWhorter, Ketrell; Bowers, K; Dolan, Lawrence; Deka, Ranjan; Jackson, Chandra; Khoury, Jane |

## VERSION 1 – REVIEW

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| **REVIEWER** | Pawel Gutaj<br>Department of Reproduction<br>Poznan University of Medical Sciences<br>Poland |
| **REVIEW RETURNED** | 26-Oct-2017 |

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| **GENERAL COMMENTS** | Thank you for this really interesting study. One thing which is lacking in the article in my opinion is a short part discussing possible causes linking excessive weight gain and LGA in women with type 1 diabetes (excessive insulin, lipids?). Why normal weight women gaining normally experienced significant reduction in LGA rates across the years, with completely opposite trend observed among overweight and obese? Could you just shortly speculate on this? Could you also suggest some new directions for future studies in the field? Do you have and access to data on diabetes duration in both cohorts? If yes you could also consider adjusting your analyses to this factor. Thank you. |

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| **REVIEWER** | Lene Ringholm<br>Center for Pregnant Women with Diabetes, Rigshospitalet University Hospital of Copenhagen, Denmark |
| **REVIEW RETURNED** | 29-Oct-2017 |

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| **GENERAL COMMENTS** | McWhorter et al aimed to evaluate whether the prevalence of large for gestational age (LGA) infants had changed over time and to identify subgroups at risk for LGA based on gestational weight gain and pre-pregnancy BMI categories.<br>This was a cross-sectional study including data from two large, but different cohorts.<br><br>They found that normal weight women with gestational weight gain within the IOM guidelines had fewer LGA infants. Pre-pregnancy BMI category did not predict LGA. |

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| | In recent years gestational weight gain has emerged as an important marker of LGA, which still occurs in approximately 50% of pregnancies among women with diabetes.<br><br>This study contributes to our understanding of the associations between gestational weight gain, pre-pregnancy BMI and LGA in women with type 1 diabetes.<br><br>There are some major areas of concern that the authors should address:<br><br>The prevalence of LGA did not differ between the PPG cohort (1978-1993) and the CSL cohort (2002-2008). Meanwhile, the prevalence of preterm delivery was 25% higher and gestational age was almost one week shorter in the CSL cohort compared to the PPG cohort, which may be ascribed a higher prevalence of cesarean section/induced labor due to LGA in the CSL cohort.<br><br>Data on HbA1c are not available. This is an important limitation because higher HbA1c in third trimester is a well-established marker of LGA (Glinianaia et al, Diabetologia 55 (2012) 3193-3203). |

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| **REVIEWER** | Christina Scifres<br>Department of Obstetrics and Gynecology<br>University of Oklahoma College of Medicine<br>United States |
| **REVIEW RETURNED** | 02-Dec-2017 |

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| **GENERAL COMMENTS** | 1. In the abstract under "Participants" would recommend changing "Pregnancies <23 weeks' gestation were excluded" to "Pregnancies delivered <23 weeks were excluded."<br>2. How was pre-pregnancy weight obtained in each cohort?<br>3. Have the ICD-9 codes for type 1 diabetes been validated?<br>4. The data in table 2 is a bit difficult to follow. For example, why are there no p values for some of the comparisons including normal weight women with weight gain under the IOM guidelines?<br>5. On page 15, lines 10-12 and in the abstract the authors state "overweight women who exceeded IOM guidelines had increased odds of LGA." However, this statement should clarify that it was overweight and obese women who were at increased risk.<br>6. Did the authors consider assessing SGA in addition to LGA? Studies have demonstrated that inadequate weight gain may increase the risk for SGA so it might be helpful to include both outcomes. |

**VERSION 1 – AUTHOR RESPONSE**

17 January 2018
Trish Groves, PhD
BMJ, Deputy Editor, BMJ
BMA House
Tavistock Square
London, WC1H9JR, UK

Dear Dr. Groves:

Thank you for your consideration of our manuscript, “The impact of gestational weight gain and pre-pregnancy body mass index on the prevalence of large-for-gestational age infants in two cohorts of women with Type I Insulin-Dependent Diabetes: A cross-sectional population study” for publication in BMJ Open. We are delighted to have the opportunity to provide revisions to the manuscript. Changes in the revised manuscript to address concerns raised are described here and highlighted in the text (where appropriate).

Reviewer: 1
Reviewer Name: Pawel Gutaj
Institution and Country: Department of Reproduction, Poznan University of Medical Sciences, Poland

1. One thing which is lacking in the article in my opinion is a short part discussing possible causes linking excessive weight gain and LGA in women with type 1 diabetes (excessive insulin, lipids?).
Thank you for requesting additional information regarding potential biological mechanisms. We agree. To respond to your concern, we added the following statement in the Background section of the manuscript on page 5: “Women with TIDM who gain excessive gestational weight have been found to be at even greater risk of LGA, perhaps due to excessive fetal nutrition resulting from increased maternal carbohydrate intake following hypoglycemic events15 . Other studies have suggested insulin resistance developing as early as in utero29 as a result of overproduction of fetal insulin in response to circulating maternal glucose crossing the placenta30. The fetus then stores this surplus energy as fat and can result in perinatal complications such as LGA18.”

2. Why normal weight women gaining normally experienced significant reduction in LGA rates across the years, with completely opposite trend observed among overweight and obese? Could you just shortly speculate on this?
Sure. Normal weight women adhering to IOM guidelines experienced a reduction in LGA rates across the years (31% in the PPG to 14% in the CSL), while LGA rates for overweight and obese women who also adhered to IOM guidelines went from 0% in the PPG to 9% (n=12) in the CSL. Women in the PPG study attended weekly clinic visits and insulin was monitored on a daily basis. Daily insulin units over gestation, adjusted for kilogram body weight for women in the PPG was similar across BMI groups (underweight, 1.2 units/kg; normal, 1.2 units/kg; overweight, 1.2 units/kg; obese, 1.0 units/kg), data not shown. Although we do not have data on insulin dosage in the CSL, TIDM treatment methods were recorded for these women, data not shown. Perhaps, if we had the insulin units/kg used by the women in the CSL, we may have observed average insulin units/kg over gestation for overweight and obese women appreciably higher than insulin units/kg for normal weight women. Higher insulin units/kg among overweight and obese women in the CSL may have accounted for the increase in LGA rates, despite this BMI subgroup’s adherence to IOM guidelines.

3. Could you also suggest some new directions for future studies in the field?
Sure. To respond to this suggestion, we have added the following text in the Conclusions section on pages 17-18, “The results of our study point to need of future research that includes additional parameters to consider when establishing appropriate GWG guidelines specific to this population, such as age at onset of diabetes (or duration), pre-pregnancy glucose control and diabetes severity upon entering pregnancy. Although in a gestational diabetes (GDM) population, Bowers et al. (Diabetologia (2013) 56:1263–1271) were also able to show racial variation in the joint effects of pre-pregnancy obesity, gestational weight gain and GDM on birthweight38. Women with TIDM who are planning pregnancies are urged to achieve optimal weight and clinically acceptable glucose control prior to pregnancy. For women in this population with unplanned pregnancies, future research is needed that examines more longitudinal studies that include regular monitoring of glucose control and insulin dosage throughout pregnancy, as well as caloric intake. Not only is GWG of key concern, but gestational timing of weight gain may also play a role in increased risk of LGA infants. Studies have demonstrated that first trimester GWG showed the strongest effect on adverse maternal, fetal and

childhood outcomes, including increased neonatal adiposity39. All of these factors should be considered when designing studies that seek to establish new GWG guidelines specific to this population."

4. Do you have any access to data on diabetes duration in both cohorts? If yes you could also consider adjusting your analyses to this factor.
Thank you for your question. Although we have access to date of diagnosis for the women in the PPG, unfortunately, we do not have access to this data for the women in the CSL cohort, prohibiting this adjustment. We acknowledge this limitation in the following statement on page 18, "Secondly, women with TIDM, when compared to women with T2DM, often have higher HbA1c throughout pregnancy due to higher diabetes duration accompanied with greater variations in glycaemic control40. We did not have access to diabetes duration for women in the CSL. However, it is plausible that diabetes duration was similar for both groups as there was no significant difference in mean maternal age at delivery between the groups for women with LGA infants across all levels of IOM adherence, data not shown".

Reviewer: 2
Reviewer Name: Lene Ringholm
Institution and Country: Center for Pregnant Women with Diabetes, Rigshospitalet University Hospital of Copenhagen, Denmark

1. The prevalence of LGA did not differ between the PPG cohort (1978-1993) and the CSL cohort (2002-2008). Meanwhile, the prevalence of preterm delivery was 25% higher and gestational age was almost one week shorter in the CSL cohort compared to the PPG cohort, which may be ascribed a higher prevalence of cesarean section/induced labor due to LGA in the CSL cohort.
Thank you for that observation. Forty-two percent (97/233) of infants in the PPG delivered by C-section were LGA and 38% (91/239) of infants in the CSL delivered by C-section were LGA (Table 3). There was an increase of deliveries prior to 37 weeks from 34% (114/333) in the PPG to 43% (152/358) in the CSL (Table 1). Overweight/obese women in the PPG accounted for only 14% (16/114) of these preterm deliveries while we observe a substantial increase in the proportion of overweight/obese women in the CSL that account for 54% (82/152) of these deliveries, data not shown. Perhaps, complications due to overweight/obesity, rather than LGA infants, contributed to the reduction in average gestational age across the years.

2. Data on HbA1c are not available. This is an important limitation because higher HbA1c in third trimester is a well-established marker of LGA (Glinianaia et al, Diabetologia 55 (2012) 3193-3203).
Good point and thank you for that statement. We acknowledged this limitation on page 18 by stating, "Our analysis was unable to include a comparison of glucose control between groups, indicated by measures of HbA1c, as this data was not available for CSL participants". Further, on page 18, "these measurements could potentially account for the reduction in LGA prevalence among normal weight women who adhered to IOM guidelines in our study."

3. The IOM guidelines for gestational weight gain apply to healthy women. It has not been established whether they are also applicable to women with diabetes. Following these guidelines in women with diabetes may result in larger infants. Secher et al (Diabetes Care 37 (2014) 2677-2684) suggested that appropriate weight gain in women with type 1 diabetes should be in the lower end of the scale of the IOM guidelines in order to obtain appropriate for gestational age infants.
Good point. We agree that the IOM guidelines may not be appropriate for this population. Our interest in this study arose out of limited research on the impact of gestational weight gain on LGA outcomes in women with TIDM. However, we acknowledge that, overall, women who adhered to IOM guidelines showed a reduction in LGA rates across the years, going from 33% in the PPG to 23% in the CSL (Table 3). We agree with Secher et al. in their suggestion to amend the guidelines to more

appropriately fit this population. Women in the PPG who adhered to IOM guidelines who had an LGA infant gained an average of 30.8 pounds (14.0 kg) compared to an average of 28.8 pounds (13.1 kg) among women who adhered to IOM guidelines who did not have an LGA infant, data not shown. On the contrary, there was no difference in average gestational weight gain among CSL women who remained within guidelines between women who had an LGA infant vs. those who did not. More studies are needed to establish an appropriate standard for gestational weight gain in this population. We address additional considerations when approaching studies that establish a more appropriate set of GWG guidelines for this population in the following statement on pages 17-18, "The results of our study point to need of future research that includes additional parameters to consider when establishing appropriate GWG guidelines specific to this population, such as age at onset of diabetes (or duration), pre-pregnancy glucose control and diabetes severity upon entering pregnancy. Although in a gestational diabetes (GDM) population, Bowers et al. were also able to show racial variation in the joint effects of pre-pregnancy obesity, GWG and GDM on birthweight38. Women with TIDM who are planning pregnancies are urged to achieve optimal weight and clinically acceptable glucose control prior to pregnancy. For women in this population with unplanned pregnancies, future research is needed that examines more longitudinal studies that include regular monitoring of glucose and insulin dosage throughout pregnancy, as well as caloric intake. Not only is gestational weight gain of key concern, but gestational timing of weight gain may also play a role in increased risk of LGA infants. Studies have demonstrated that first trimester gestational weight gain showed the strongest effect on adverse maternal, fetal and childhood outcomes, including increased neonatal adiposity39. All of these factors should be considered when designing studies that seek to establish new GWG guidelines specific to this population."

4. Women with diabetic nephropathy and/or retinopathy were excluded. This may affect study results because these women comprise a large proportion of the population of pregnant women with diabetes.
We did not exclude these women. Rather, we were unable to adjust for these factors as described (and corrected) in the limitations section on page 19, "Lastly, despite the importance of nephropathy and retinopathy as indicators of diabetes severity, potentially affecting glucose transport, differing definitions between cohorts prevented variable harmonization and, therefore, prohibited the adjustment of these factors in our study."

5. As the authors state in the list of strengths and limitations, the generalizability of the study findings is limited.
Thank you for your comment. We acknowledge that there are aspects of this study that limit its generalizability, as described in the following statement on pages 18-19, "The differences between the populations, which include regional differences in diet, methods of treatment, access to quality health care, racial composition and geography limit the generalizability of our results." However, most studies that examine pregnancy among women with established diabetes focus on T2DM. We believe our study, with its emphasis on exclusively TIDM, adds to the literature and as previously stated, contributes to our understanding of gestational weight gain, pre-pregnancy BMI and LGA in this population.

Reviewer: 3
Reviewer Name: Christina Scifres
Institution and Country: Department of Obstetrics and Gynecology, University of Oklahoma College of Medicine, United States

1. In the abstract under "Participants" would recommend changing "Pregnancies <23 weeks' gestation were excluded" to "Pregnancies delivered <23 weeks were excluded."
We agree and have changed the text to read "Pregnancies delivered prior to 23 weeks' gestation were excluded."

2. How was pre-pregnancy weight obtained in each cohort?
Thank you for your question. Pre-pregnancy weight was determined by self-reported weight prior to pregnancy for both cohorts (pg 8). We have now acknowledged this as a limitation in the following statement on page 19, "In addition, pre-pregnancy BMI was determined, in part, by self-reported pre-pregnancy weight in both cohorts, yielding our calculation of pre-pregnancy BMI subject to recall bias."

3. Have the ICD-9 codes for type 1 diabetes been validated?
Thank you for your question. We have added the following text in the Limitations section on page 19 of this manuscript, "The ICD-9 codes that were used to identify women in the CSL with TIDM have not been validated in this study. However, according to Zhang et al., (Am J Obstet Gynecol. 2010 Oct; 203(4): 326.e1–326.e10.) validation studies were conducted for four key outcomes, including method of delivery, gestational age ≥34 and ≥37 weeks and clinical diagnosis of shoulder dystocia34, common in LGA deliveries. Most variables that were reviewed were highly accurate, indicating information provided in the validation studies was reliable and likely generalizable to the entire database."

4. The data in table 2 is a bit difficult to follow. For example, why are there no p values for some of the comparisons including normal weight women with weight gain under the IOM guidelines?
In response to your concern, we have corrected the presentation of Table 2, including condensing IOM adherence labels and reflecting all chi-square p-values for LGA proportions of women by pre-pregnancy BMI and IOM adherence for both cohorts.

5. On page 15, lines 10-12 and in the abstract the authors state "overweight women who exceeded IOM guidelines had increased odds of LGA." However, this statement should clarify that it was overweight and obese women who were at increased risk.
Thank you for this observation. ORs represented in Table 5 include combined BMI subgroups overweight/obese for PPG. However, due to sufficient sample sizes in the CSL, overweight and obese subgroups were not combined and ORs are represented separately for each group. Therefore, the statement, "overweight women who exceeded IOM guidelines [OR 2.35 95%CI (1.26, 4.40), p=0.01] had increased odds of LGA" exclusively refers to the overweight subgroup.

6. Did the authors consider assessing SGA in addition to LGA? Studies have demonstrated that inadequate weight gain may increase the risk for SGA so it might be helpful to include both outcomes.
Yes. We considered assessing SGA in addition to LGA. There were 18 in the CSL cohort, 5 under, 6 within and 7 over IOM guidelines, p=0.25). However, in the PPG cohort, there were only 2 SGA infants, both of mothers who were under IOM guidelines. The small sample size in PPG did not allow us to examine a change in SGA rates across the years.

We hope that the concerns raised in this review have been adequately addressed. Thank you for your consideration of this revised manuscript. We look forward to your decision.

Sincerely,

Ketrell L. McWhorter, PhD, MS (on behalf of all authors)
Postdoctoral Research Fellow

**VERSION 2 – REVIEW**

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| **REVIEWER** | Paweł Gutaj<br>Dept. of Reproduction. Poznan University of Medical Sciences Poland |
| **REVIEW RETURNED** | 19-Jan-2018 |

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| **GENERAL COMMENTS** | Thank you. |

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| **REVIEWER** | Lene Ringholm<br>Center for Pregnant Women with Diabetes, Rigshospitalet University Hospital of Copenhagen, Denmark |
| **REVIEW RETURNED** | 04-Feb-2018 |

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| **GENERAL COMMENTS** | Thank you for carefully answering my comments and revising the manuscript accordingly. |

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| **REVIEWER** | Christina Scifres<br>University of Oklahoma College of Medicine, USA |
| **REVIEW RETURNED** | 11-Feb-2018 |

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| **GENERAL COMMENTS** | The authors have done an excellent job of responding to the review concerns, and the manuscript is much improved after their edits. |